

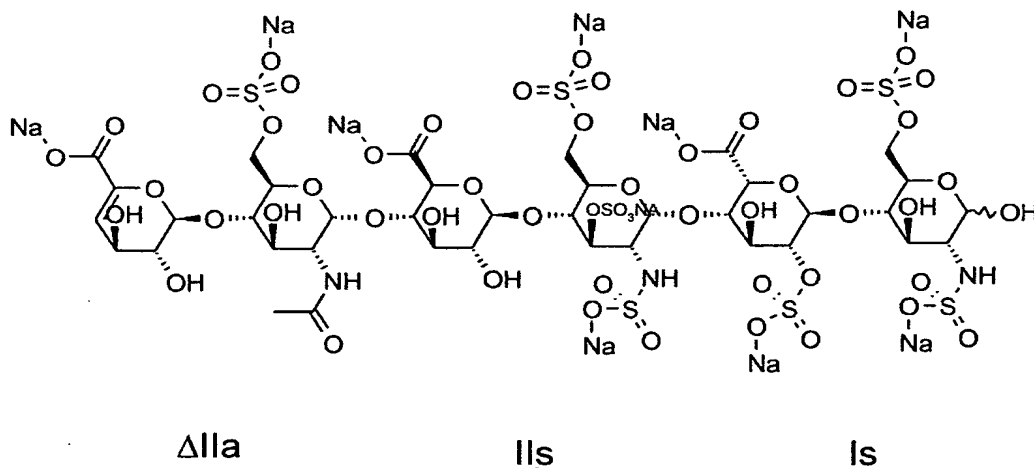
CLAIMS

1. A mixture of sulfated oligosaccharides having the general structure of the constituent polysaccharides of heparin and having the following characteristics:

- a mean molecular weight of 1500 to 3000 daltons, an anti-Xa activity of 120 to 200 IU/mg, an anti-IIa activity of less than 10 IU/mg and an anti-Xa activity/anti-IIa activity ratio of greater than 30,

wherein the constituent oligosaccharides of said mixtures:

- contain 2 to 26 saccharide units,
- have a 4,5-unsaturated uronic acid 2-O-sulfate unit at one of their ends,
- contain the hexasaccharide Δ IIa-II $\underline{s}$ -Is of formula:



and are in the form of an alkali or alkaline-earth metal salt.

2. A mixture of oligosaccharides as claimed in claim 1, wherein the alkali or alkaline-earth metal salt is selected from sodium, potassium, calcium and magnesium salts.

3. A mixture of oligosaccharides as claimed in claim 1, which contains a hexasaccharide fraction representing from 15 to 25% of the mixture of oligosaccharides.

5 4. A mixture of oligosaccharides as claimed in claim 3, wherein from 8 to 15% of the hexasaccharide fraction of the mixture of oligosaccharides is said Δ IIa-II $\underline{s}$ -Is hexasaccharide.

10 5. A mixture of oligosaccharides as claimed in claim 1, which exhibits an anti-Xa activity of between 150 IU/mg and 200 IU/mg.

15 6. A mixture of oligosaccharides as claimed in claim 1, which has an anti-IIa activity of less than 5 IU/mg.

7. A mixture of oligosaccharides as claimed in claim 1, which exhibits an anti-Xa activity/anti-IIa activity ratio greater than 50.

20 8. A mixture of oligosaccharides as claimed in claim 1, which has a mean molecular weight of between 2000 and 3000 Daltons.

25 9. A mixture of oligosaccharides as claimed in claim 1, which exhibits an anti-Xa activity of between 150 and 200 IU/mg, an anti-IIa activity of between 0.5 and 3.5 IU/mg, and a mean molecular weight of between 2400 and 2650 Da.

30 10. A mixture of oligosaccharides as claimed in claim 6, which exhibits an anti-Xa activity of 0.5 to 3.5 IU/mg.

11. A mixture of oligosaccharides as claimed in claim 7, which exhibits an anti-Xa activity/anti-IIa activity ratio of greater than 100.

12. A mixture of oligosaccharides as claimed in claim 8, which has a mean molecular weight of from 2400 to 2650 Daltons.

13. A method for preparing mixtures of oligosaccharides as claimed in claim 1, which method includes the step of depolymerising the quaternary ammonium salt of the benzyl ester of heparin in an organic medium in the presence of a strong organic base with a pKa greater than 20, wherein the organic base used is selected from the family of phosphazenes and is dissolved in said organic medium, and the water content of the reaction medium is less than 0.6%.

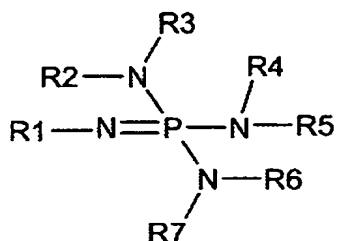
14. The method of claim 13 wherein said organic medium is dichloromethane.

15. The method of claim 13 wherein the water content is less than 0.3%.

16. The method of claim 15 wherein the water content is less than 0.2%.

17. The method of claim 13 wherein said quaternary ammonium salt of the benzyl ester of heparin is the benzethonium, cetylpyridinium or cetyltrimethylammonium salt.

18. The method of claim 13, wherein the bases of the family of phosphazenes are selected from those of formula:



in which the radicals R1 to R7 are identical or different and represent linear or branched alkyl radicals containing from 1 to 6 carbon atoms.

5 19. The method of claim 13, wherein the strong base/ester mol ratio is between 0.2 and 5.

20. The method of claim 19, wherein the strong base/ester mol ratio is between 0.6 and 2.

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21. A method for preparing oligosaccharides as claimed in claim 1 from heparins, comprising the steps of:

- a) transalification of sodium heparin by the action of benzethonium chloride,
- 15 b) esterification of benzethonium heparinate obtained by the action of benzyl chloride,
- c) transalification of the benzyl ester obtained and obtaining of the quaternary ammonium salt,
- d) depolymerization of the quaternary ammonium salt of the
20 benzyl ester of heparin by the method as defined in claim 13,
- e) conversion of the quaternary ammonium salt to a sodium salt.

25 22. The method of claim 21, further comprising the step of f) saponification of the heparin by the action of a base.

23. The method of claim 22 wherein said base is sodium hydroxide.

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24. The method of claim 21, further comprising the step of g) purification.

25. the method of claim 24 wherein said purification step is effected by the action of an oxidizing agent.

26. The method of claim 25 wherein said oxidizing agent is
5 hydrogen peroxide.

27. The method of claim 21, wherein the reaction of step a) is carried out by the action of benzethonium chloride in excess, on sodium heparin, at a temperature in the region of 15 to
10 25°C, with a salt/ sodium heparin molar ratio of between 3 and 4.

28. The method of claim 21, wherein the esterification of step b) is carried out in a chlorinated organic solvent, at a
15 temperature of between 25 and 45°C, and the ester in the form of a sodium salt is then recovered by precipitation by means of sodium acetate at 10% by weight in an alcohol in a proportion of 1 to 1.2 volumes of alcohol per volume of reaction medium.

20 29. The method of claim 28 wherein said chlorinated organic solvent is chloroform or dichloromethane. 30. The method of claim 28 wherein said temperature is between 30 and 40°C.

30. The method of claim 28 wherein said alcohol is methanol.
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31. The method of claim 21, wherein the degree of esterification of the quaternary ammonium salt of the benzyl ester of heparin is between 50 and 100%.

30 32. The method of claim 31 wherein said degree of esterification is between 70 and 90%.

33. The method of claim 21, wherein 0.5 to 1.5 parts by weight of benzyl chloride per 1 part by weight of benzethonium salt of heparin are used and the reaction time is between 10 and 35 h.

5 34. The method of claim 21, wherein the transalification of step c) is carried out by means of a quaternary ammonium chloride, in an aqueous medium at a temperature between 10 and 25°C.

10 35. The method of claim 34 wherein said quaternary ammonium chloride is selected from benzethonium chloride, cetylpyridinium chloride and cetyltrimethylammonium chloride.

36. The method of claim 34 wherein the mol ratio of quaternary
15 ammonium chloride/sodium salt of the benzyl ester of heparin is between 2 and 3.

37. The method of claim 21 wherein the conversion to a sodium
salt of the quaternary ammonium salt of the benzyl ester of
20 depolymerized heparin (step e) is carried out by treating the reaction medium with an alcoholic solution of sodium acetate at a temperature between 15 and 25°C.

38. The method of claim 37 wherein said alcoholic solution is a
25 10% solution of sodium acetate in methanol (weight/volume).

39. The method of claim 21 wherein the saponification (step f) is carried out by means of an alkali metal hydroxide, in an aqueous medium, at a temperature between 0 and 20°C.

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40. The method of claim 39 wherein said alkali metal hydroxide is selected from sodium hydroxide, potassium hydroxide and lithium hydroxide.

41. The method of claim 39 wherein said temperature is between 0 and 10°C.

42. The method of claim 39, wherein 1 to 5 molar equivalents of alkali metal hydroxide are used.

43. The method of claim 42 wherein 1 to 2 molar equivalents of said sodium hydroxide are used.

44. The method of claim 21, wherein the purification (step g) is carried out by means of hydrogen peroxide, in an aqueous medium, at a temperature of 10 to 50°C.

45. The method of claim 44 wherein said temperature is between 20 and 40°C.

46. A medicament comprising the oligosaccharides as claimed in claim 1.

47. The medicament of claim 46 which has antithrombotic activity.

48. A method for the prevention or treatment of a condition selected from venous and arterial thromboses, deep vein thrombosis, pulmonary embolism, unstable angina, myocardial infarction, cardiac ischemia, occlusive diseases of the peripheral arteries and atrial fibrillation, the proliferation of smooth muscle cells, atherosclerosis and arteriosclerosis, cancer by modulating angiogenesis and growth factors, and diabetic disorders such as diabetic retinopathies and nephropathies comprising administering to a patient in need thereof an effective amount of a medicament of claim 47.

49. A pharmaceutical composition containing at least one medicament as defined in claim 47 and one or more pharmaceutically inert excipients or vehicles or additives.

5 50. A pharmaceutical composition as claimed in claim 49 in the form of solutions for injection by the subcutaneous or intravenous route.

10 51. A pharmaceutical composition as claimed in claim 49 in the form of a formulation for inhalation intended for the pulmonary route.

52. A pharmaceutical composition as claimed in claim 49 in the form of a formulation for administration by the oral route.

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53. A mixture of polysaccharides as defined in claim 1 when obtained by the method of claim 21.